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ORIGINAL ARTICLE



## Efficacy and safety of ossein-hydroxyapatite complex versus calcium carbonate to prevent bone loss

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### ABSTRACT

**Objective:** This study aimed to compare the efficacy and safety of ossein-hydroxyapatite complex (OHC) versus calcium carbonate (CC) for preventing bone loss during perimenopause in current clinical practice.

**Methods:** The prospective, comparative, non-randomized, open-label study included 851 perimenopausal women with basal bone mineral density (BMD) T-score  $\geq -2$  standard deviations (SDs). Participants received either OHC (712 mg calcium/day) or CC (1000 mg calcium/day) over 3 years. BMD was evaluated by dual-energy X-ray absorptiometry at the lumbar spine (L2–L4) at baseline and after 18 and 36 months of follow-up. Adverse drug reactions (ADRs) were also recorded.

**Results:** In women receiving OHC, BMD at the L2–L4 site remained stable over the 3-year follow-up period (mean [SD] change 0.00 [0.11] g/cm<sup>2</sup>). BMD in the CC arm decreased  $-3.1\%$  (mean [SD]  $-0.03$  [0.11] g/cm<sup>2</sup>). Between-group differences were statistically significant ( $p < 0.001$ ) and favored OHC. ADRs were more frequent in the CC group (7.7% vs. 2.7% in the OHC group;  $p = 0.001$ ), affecting primarily the gastrointestinal system.

**Conclusion:** OHC showed greater efficacy and tolerability than CC for bone loss prevention in perimenopausal women in real-world practice. As the daily dose of calcium was higher in the CC group, the differences might be linked to the ossein compound in OHC.

### ARTICLE HISTORY

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Osteoporosis; ossein-hydroxyapatite complex; calcium carbonate; perimenopause; osteopenia; bone loss; safety; efficacy

### Introduction

The World Health Organization describes osteoporosis as a 'progressive systemic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture'<sup>1</sup>. The increased rate of fractures associated with the disease is one of the most common causes of disability and a major contributor to medical care costs in many regions of the world<sup>2</sup>. A recent systematic review showed that insufficient calcium intake is a worldwide health problem with potentially serious consequences, particularly in women and especially given the aging of the population<sup>3</sup>.

Research on osteoporosis in women has focused primarily on the postmenopausal and elderly period. Nevertheless, an accelerated rate of bone loss has also been reported during the menopausal transition<sup>4,5</sup>, when estrogen secretion is markedly reduced particularly in the year before the final menstrual period and the first 2 years thereafter<sup>6</sup>.

Calcium, at a recommended daily intake of 700–1200 mg<sup>7,8</sup>, is an important adjunctive therapy for the treatment and prevention of osteoporosis when dietary intake is insufficient<sup>7–9</sup>. Meta-analysis has shown it to be more effective than placebo in reducing bone loss by the second year of treatment<sup>10</sup>, and that it has a positive effect on bone mineral density (BMD) and a tendency to reduce fracture incidence.

Calcium carbonate (CC) is one widely used calcium supplement when the recommended dietary calcium intake is insufficient. Another supplement is ossein-hydroxyapatite complex (OHC), which has also been shown to be effective in maintaining BMD and to have a more intense osteogenic effect than a calcium supplement alone after oral administration<sup>11–18</sup>. OHC consists of ossein, the protein that forms the organic matrix of bone, and hydroxyapatite (Ca<sub>5</sub>[PO<sub>4</sub>]<sub>3</sub>OH), the most relevant bone salt of vertebrate bone.

Little is known about the comparative effectiveness of calcium supplements in the perimenopausal period. However,

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\*In memoriam.

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based on results from clinical trials<sup>14–18</sup>, our hypothesis was that OHC might also be more effective than CC at preventing bone loss in perimenopause. The aim of the present study was therefore to compare the efficacy, safety, and tolerability of OHC versus CC in preventing bone loss in perimenopausal women over a 3-year treatment period in conditions of usual clinical practice.

## Methods

### Study design and population

The PRevention of the Osteoporosis at the Perimenopausal period (PROP) trial (ISRCTN83573042) was a Strengthening The Reporting of OBservational Studies in Epidemiology (STROBE)-compliant observational, prospective, multicenter, open-label study performed between 2005 and 2014 in accordance with the Declaration of Helsinki (2004) and local legislation on data protection. Participants were followed for up to 3 years and made a total of seven study visits (baseline and 6, 12, 18, 24, 30, and 36 months).

Participants were recruited consecutively in outpatient gynecology clinics around Spain. As safety was one of the main objectives of the study, and due to the relatively limited amount of tolerability data available for OHC, it was planned to include participants at a ratio of 3:1 for OHC and CC, respectively. Women were eligible to participate if they met the following criteria: 40–50 years of age; perimenopausal at study commencement; and lumbar or hip BMD  $T$ -score  $\geq -2$  standard deviations (SDs) (normal BMD or mild osteopenia) measured using dual-energy X-ray absorptiometry (DXA) likely, in the opinion of the attending clinician, to benefit from calcium supplementation. A participant was considered perimenopausal if she reported menstrual irregularity lasting less than 12 consecutive months not necessarily associated with menopausal symptoms such as hot flashes, vaginal dryness, or night sweats.

Patients were excluded if they had osteoporosis (BMD  $T$ -score  $\leq -2.5$  SDs diagnosed using DXA) or severe osteopenia (BMD  $T$ -score  $< -2$  SDs), if they were being treated with drugs with a known effect on bone metabolism (glucocorticoids, steroids, thyroid hormones, heparin [long-term treatment], anticonvulsants, contraceptives, hormone replacement therapy, lithium, cancer chemotherapy, selective estrogen receptor modulators, calcium supplements, vitamin D, immunosuppressive therapy, or bisphosphonates), or if they had a diagnosis of hypercalcemia, hypercalciuria, or neoplasia during the previous 5 years or osteomalacia, Paget bone disease, or diseases affecting bone metabolism. Pregnant women, as well as those with reporting hypersensitivity to any of the study drugs, or participants with gastrointestinal disturbances that could interfere with drug absorption, were also excluded.

Following a prescreening visit, all selected patients underwent bone densitometry using DXA. Patients meeting the selection criteria were included in the study after providing informed consent.

Given that this was an observational study performed under conditions of current clinical practice, no formal

sample size calculation was carried out. However, upon completion of the study, statistical power was calculated based on the final number included and results from previous studies<sup>17</sup>, and was found to be sufficient to detect a difference between the two treatment groups of at least 2% in lumbar BMD after 3 years with a power of 85% and a significance level of 5%, using the Student  $t$ -test for independent data.

### Treatment

Based on the criteria of the participating clinicians, participants received either OHC at a dose of two 830-mg tablets every 12 h (712 mg of elemental calcium per day) or CC at a dose of a single 1250-mg tablet every 12 h (equivalent to a total daily dose of 1000 mg of elemental calcium).

Of note, a single 830-mg OHC tablet (Osteopor<sup>®</sup>/Ossopan<sup>®</sup>/Osteogenon<sup>®</sup>/Totalos Plus<sup>®</sup>; Pierre Fabre Médicament, Castres, France) contains calcium (178 mg), phosphorus (82 mg), and proteins associated with bone metabolism (osteocalcin, 5.8  $\mu$ g; type I collagen, 216 mg; insulin growth factor type I, 168 ng; insulin growth factor type II, 84 ng; transforming growth factor- $\beta$ , 21 ng).

### Assessments

Change in BMD was measured by DXA at the lumbar spine (L2–L4) at baseline and after 18 and 36 months of follow-up. When possible, BMD assessments for the femoral neck, trochanter, Ward's triangle, and total hip were also sought. All bone densitometries (baseline and follow-up) were performed at the nearest reference center for each patient.

Adverse drug reactions (ADRs) associated with the treatments were recorded, as well as the number of patients with dose reduction due to toxicity and the number of patients withdrawing due to treatment intolerance. Participating clinicians directly questioned patients on the presence of ADRs and recorded their severity, duration, potential relation with the study drug, action taken, and outcome.

The presence of fractures, the body mass index, and risk factors for bone loss were recorded at the baseline visit. Daily dietary calcium intake was estimated using a questionnaire to record weekly average consumption of the most frequent food products.

At follow-up clinic visits, in addition to DXA assessments, changes in concomitant medication, withdrawal from treatment, and treatment compliance were recorded. Treatment compliance was evaluated at each 6-month follow-up visit by clinician interview. Patients were asked whether they took the medication daily and whether they took the medication at the prescribed dose. Possible responses for both questions were: 1 = 'Never', 2 = 'Almost never', 3 = 'Almost always', and 4 = 'Always'. Patients were categorized as compliant ( $>70\%$  of doses taken) if they answered 'Almost always' or 'Always' to both questions.

### Statistical analysis

Descriptive statistics used absolute values and proportions, means, or medians as appropriate, together with measures

of central tendency (SDs and interquartile ranges). Baseline characteristics for the two treatment groups were compared using Student's *t*-test or the Mann-Whitney test and the chi-square or Fisher's exact test as appropriate.

The safety analysis was conducted on the safety population, defined as all participants who took at least one dose of the study medication. The cumulative incidence of each type of ADR by cohort was estimated by dividing the number of patients with at least one recorded ADR by the total number of exposed participants over the study. Cumulative incidences were compared between groups using the chi-square or Fisher's exact test.

The initial efficacy analysis was performed in the full analysis set; that is, patients who fulfilled all selection criteria, had taken the prescribed treatment with any degree of compliance, and had at least one efficacy assessment. A second efficacy analysis was performed using data from patients with an average compliance of 70% or more. The analysis was then repeated in both the overall and compliant-only populations after excluding patients who began taking any of the concomitant treatments described in the exclusion criteria (e.g. hormone replacement therapy, contraceptives, or isoflavones) while in the study. Treatment compliance was also analyzed and compared across study arms.

Change in bone mass was assessed based on mean DXA scores and expressed in grams per square centimeter and as *T*-scores. Paired *t*-tests or Wilcoxon tests were used as appropriate to assess the statistical significance of any changes.

Analyses were performed using SAS v9.4 (SAS Institute Inc, Cary, NC, USA), and all tests were two-sided with a significance level of 0.05.

Results

A total of 1032 women were considered eligible for inclusion in the study (Figure 1). Of these, 181 were excluded from analysis because they failed to present at the first follow-up visit (*n* = 127 [16.8%] in the OHC group and *n* = 54 [19.6%] in the CC group). Data from 851 women were therefore available for the safety analysis (*n* = 629 in the OHC group and *n* = 222 in the CC group). Of those who began the study, 722 (69.9%) patients completed 1 year of follow-up, 534 (51.7%) patients completed 2 years, and 437 (42.3%) patients completed 3 years. Reported reasons for discontinuation in the OHC and CC groups, respectively, were: loss to follow-up, 83% and 61%; concomitant disease, 10% and 6%; and adverse effects, 7% and 33%.

For the efficacy analysis, 845 patients (99.3%) were included in the full analysis set (624 in the OHC group and 221 in the CC group); 487 (57.6%) patients were eligible for treatment-compliant analysis (*n* = 355 of the 624 patients [56.9%] in the OHC group and 132 of the 221 patients [59.7%] in the CC group). A total 57.6% (*n* = 487) of patients reported a level of compliance, representing over 70% of theoretical doses, with no statistically significant differences between treatment groups.

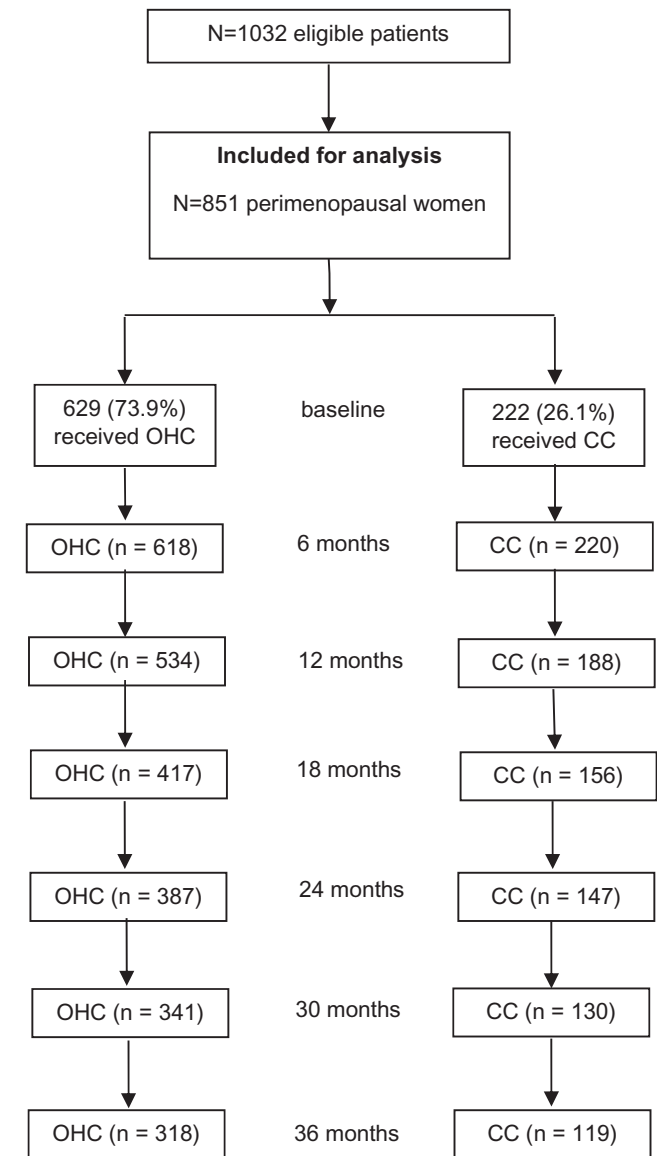


Figure 1. Study flow chart. CC, calcium carbonate; OHC, ossein-hydroxyapatite complex.

There were no significant differences between the OHC and CC groups for any of the baseline variables studied (Table 1).

Change in bone mineral density

Table 2 presents the baseline BMD at the lumbar spine (L2–L4) and the change after 36 months of treatment in the full analysis set population. The mean (SD) *T*-score in the CC group decreased by −0.23 (0.76) over the study period, compared to 0.01 (0.82) in the OHC group (difference in change scores significant at *p* < 0.001). Over the same period, bone density decreased by a mean (SD) of −0.03 (0.11) g/cm<sup>2</sup> in the CC group but remained stable in the OHC group (mean [SD] change 0.00 [0.11] g/cm<sup>2</sup>), with the difference significant at *p* < 0.001 (Figure 2). After 3 years of treatment, bone loss in the CC arm was 3.1% as shown

**Table 1.** Baseline characteristics of the two study groups.

Variable	OHC (n = 629)	CC (n = 222)	p-Value
Age (years), mean (SD)	47.3 (3.0)	47.1 (2.8)	0.485
Number of children (range 0–12), mean (SD)	1.9 (1.0)	1.9 (1.2)	0.627
Concomitant treatment (not calcium supplements), n (%)	131 (20.8)	41 (18.5)	0.452
Age at menarche (years), mean (SD)	12.2 (1.4)	12.3 (1.4)	0.268
Past contraceptive treatment, n (%)	213 (42.6)	86 (45.7)	0.458
Duration (years), mean (SD)	7.0 (4.4)	6.6 (4.5)	0.572
Menstrual cycle			
Regular (last 12 months), n (%)	191 (30.9)	70 (32.3)	0.531
Periodicity changes (last 3 months), n (%)	228 (36.9)	71 (32.7)	0.452
Amenorrhea (last 3–11 months), n (%)	199 (32.2)	76 (35)	0.458
Risk factors (habits)			
Smoking status			
Current smoking, n (%)	172 (27.9)	73 (33.2)	0.137
Cigarettes per day, mean (SD)	13.5 (8.4)	14.1 (7.5)	0.583
Smoking habit (years), mean (SD)	19.8 (7.9)	18.1 (8.7)	0.157
Former smoker, n (%)	60 (23.4)	16 (19.3)	0.429
Years after smoking cessation, mean (SD)	8.6 (6.5)	11.6 (6.4)	0.108
Frequent alcohol use	47 (7.9)	19 (8.6)	0.732
Drinks a day (units), mean (SD)	1.50 (0.76)	1.42 (0.51)	0.681
Caffeine use, n (%)	249 (44.6)	100 (50.3)	0.171
Reported calcium intake (mg/day), mean (SD)	992 (503)	996 (475)	0.973
Regular exercise, n (%)	226 (44.1)	92 (47.9)	0.358

CC, calcium carbonate; OHC, ossein-hydroxyapatite complex; SD, standard deviation.

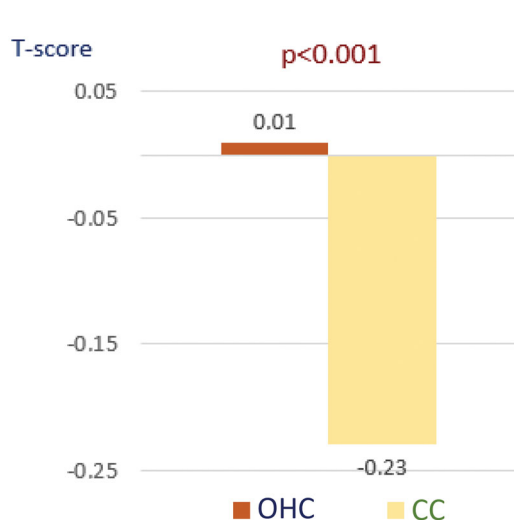
**Table 2.** Evolution of bone mineral density (T-scores and grams per square centimeter) at the lumbar spine (n = 807).

Visit	Ossein-hydroxyapatite complex			Calcium carbonate			Between-group p-Value <sup>b</sup>
	n	Mean (SD)	p-Value <sup>a</sup>	n	Mean (SD)	p-Value <sup>a</sup>	
T-score							
Baseline	601	−0.61 (1.11)	–	206	−0.75 (0.98)	–	0.250
V7 – baseline	299	0.01 (0.82)	0.19	107	−0.23 (0.76)	0.001	<0.001
BMD (g/cm <sup>2</sup> )							
Baseline	578	1.03 (0.15)	–	204	1.01 (0.13)	–	0.057
V7 – baseline	280	0.00 (0.11)	0.34	102	−0.03 (0.11)	<0.001	<0.001

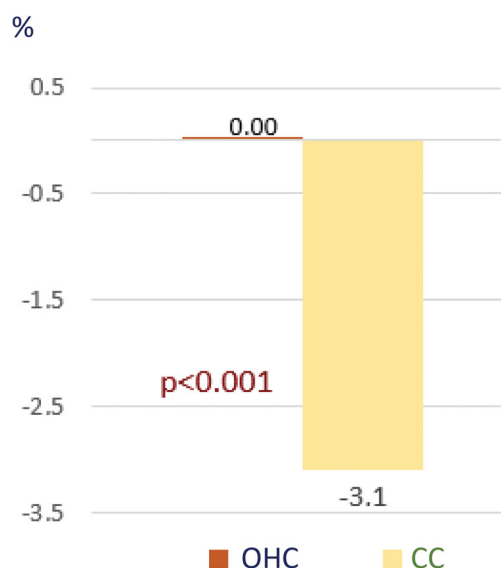
BMD, bone mineral density; SD, standard deviation; V7, visit at 36 months of follow-up.

<sup>a</sup>Wilcoxon test for change from baseline within groups.

<sup>b</sup>Mann–Whitney U-test for difference between treatment groups.



**Figure 2.** Lumbar T-score change (mean) from baseline in the study arms (L2–L4). CC, calcium carbonate; OHC, ossein-hydroxyapatite complex.



**Figure 3.** Mean percentage change from baseline in the study arms (L2–L4). CC, calcium carbonate; OHC, ossein-hydroxyapatite complex.

in **Figure 3** ( $p < 0.001$  for the difference between study groups).

Changes in T-score and percentage changes at the lumbar site are illustrated graphically for the two groups in **Figures 2** and **3**.

### Calcium consumption

The mean (SD) daily calcium consumption for the full sample was estimated at 993 ( $\pm$  495) mg with no significant



differences between the arms (Table 1). There was considerable variability in intake among participants, with 12.2% of the patients having a daily intake  $\leq 500$  mg, 22.4% between 501 and 800 mg, 18.9% between 801 and 1000 mg, 33.6% between 1001 and 1500 mg, and 12.8% of the patients with intake  $>1500$  mg.

### Subgroup analysis

After excluding patients who began taking any treatment described in the exclusion criteria section after study initiation, lumbar BMD results in the remaining population ( $n=672$ ) showed a mean (SD)  $T$ -score increase of 0.09 (0.79) in the OHC arm ( $n=224$ ) and a decrease of  $-0.23$  (0.70) in the CC group ( $n=76$ ) by study end ( $p<0.001$  for between groups differences). The mean (SD) change for this subgroup was 0.01 (0.11) g/cm<sup>2</sup> in the OHC arm, which represented an increase of 0.96%, compared to a mean change of  $-0.03$  (0.10) g/cm<sup>2</sup>, or a decrease of  $-3.1\%$ , in the CC group ( $p<0.001$  for difference between arms).

BMD results were similar when the analyses were re-run in compliant patients ( $n=487$ ), with OHC patients ( $n=281$ ) showing a mean (SD) increase in lumbar  $T$ -score of 0.03 (0.80) and CC patients ( $n=101$ ) showing a mean decrease of  $-0.27$  (0.72) ( $p<0.0001$  between groups). The mean (SD) change in compliant patients was 0.00 (0.11) g/cm<sup>2</sup>, or no change, in the OHC arm and a decrease of  $-0.03$  (0.10) g/cm<sup>2</sup> in the CC group, representing a change of  $-3.1\%$  ( $p<0.001$  for the between-group difference).

Finally, in compliant patients who took no drugs which could potentially affect BMD other than the study drugs ( $n=361$ ), by study end there was a mean (SD) change in lumbar  $T$ -score of 0.10 (0.79) in the OHC arm ( $n=214$ ) and a change of  $-0.27$  (0.69) in the CC arm ( $n=71$ ). The difference in the size of the change between groups was statistically significant at  $p<0.0001$ . In the same population, the mean (SD) change was 0.01 (0.11) g/cm<sup>2</sup> in the OHC arm, which represented an increase of 0.96%, compared to  $-0.03$  (0.10) g/cm<sup>2</sup> in the CC group, which represented a change of  $-3.1\%$  ( $p<0.001$  for the difference between groups).

### Patients with osteoporosis at study end

In patients who took no drugs which could potentially affect BMD except for the study drugs ( $n=672$ ), the BMD test results indicated the presence of osteoporosis in 0.8% ( $n=4$ ) of the OHC group and in 3.0% ( $n=5$ ) of the CC arm ( $p<0.05$  for the between-group difference).

Similar results were observed in the same group when only compliant patients were evaluated ( $n=361$ ), with 1.5% ( $n=4$ ) in the OHC arm and 5.6% ( $n=5$ ) in the CC group showing osteoporosis ( $p<0.05$  for the difference between groups).

### Reported fractures by treatment group

No clinical vertebral fractures were reported during follow-up. However, 19 patients (2.3%) suffered a bone fracture

Table 3. Reported adverse drug reactions.

Adverse drug reaction (ADR)	OHC ( $n=629$ )	CC ( $n=222$ )	p-Value
Total affected patients*	17 (2.7)	17 (7.7)	0.001
Patients with gastrointestinal complaints <sup>a</sup>	13 (2.1)	13 (5.9)	0.005
Headache	3 (0.5)	1 (0.5)	1.000 <sup>b</sup>
Dizziness	0	1 (0.5)	0.261 <sup>b</sup>
Dysgeusia	0	1 (0.5)	0.261 <sup>b</sup>
Back pain	0	1 (0.5)	0.261 <sup>b</sup>
Eczema	1 (0.2)	0	1.000 <sup>b</sup>
Weight gain	1 (0.2)	0	1.000 <sup>b</sup>
Dry mouth	1 (0.2)	1 (0.5)	0.454 <sup>b</sup>

Data presented as  $n$  (%).

CC, calcium carbonate; OHC, ossein-hydroxyapatite complex.

<sup>a</sup>Including dyspepsia, abdominal pain, flatulence, vomiting, and esophagitis.

<sup>b</sup>Not statistically significant.

\*A patient could report more than one ADR.

which, in most cases, was assumed to be caused by high-impact trauma. The rate was higher in the CC group at 3.7% ( $n=8$ ), compared to 1.8% ( $n=11$ ) in the OHC group, although the difference was not statistically significant.

### Tolerability

A total of 34 patients reported at least one ADR (see Table 3) ( $n=17$  in each group, or 2.7% and 7.7% for the OHC and CC group, respectively;  $p=0.001$ ). ADRs were considered mild. A total of 10 patients withdrew from the study because of ADRs; two (0.3%) in the OHC group and eight (3.6%) in the CC group ( $p<0.001$ ).

The majority of ADRs were gastrointestinal: 13 patients (2.1%) in the OHC group and 13 (5.9%) in the CC group reported gastrointestinal ADRs at some point in the study ( $p<0.005$ ). No cardiovascular events were reported.

### Discussion

To our knowledge, this is the first study to comparatively evaluate the long-term efficacy, safety, and tolerability of OHC versus CC for bone loss prevention during perimenopause.

Lumbar BMD was maintained in patients treated with OHC but decreased significantly (3.1%) over the 3-year follow-up period in patients treated with CC.

The results observed here are similar to those reported in previous studies comparing OHC and CC. In a randomized, open-label, 2-year follow-up study carried out in non-osteoporotic postmenopausal women<sup>17</sup>, patients treated with OHC maintained their BMD while patients treated with CC had a 3.7% BMD loss by the study end. Similar trends were observed in trials comparing the two drugs in postmenopausal women with<sup>18</sup> or without<sup>15</sup> bone fractures and in elderly patients with osteoporosis<sup>14,19</sup>. In a meta-analysis of randomized controlled trials which compared OHC and CC, OHC proved to be substantially more effective in preventing bone loss than CC<sup>13</sup>.

The difference in efficacy between the two calcium supplements does not seem to be related exclusively to the dose of calcium supplementation, as the amount of calcium provided by CC was 40.4% higher than that provided by OHC.

The difference in efficacy might be explained by the osteogenic effects associated with OHC's organic component, ossein, as suggested by several authors<sup>11,12,15,20</sup>.

Proteins present in OHC (osteocalcin, insulin growth factor type I, insulin growth factor type II, transforming growth factor- $\beta$ ) are considered mitogenic for bone cells *in vitro*<sup>21–23</sup> and could improve bone formation *in vivo* as observed in different studies<sup>11,12,14,15</sup>, although the process is not completely understood.

The osteogenic hypothesis seems to be confirmed by the results of a randomized controlled trial which compared the effects of OHC and CC on bone metabolism in women with osteoporosis aged >65 years without prevalent fractures<sup>14</sup>. After 3 years of treatment, it was observed that mean levels of serum osteocalcin significantly increased in patients treated with OHC in comparison with those receiving CC, indicating a greater anabolic effect of OHC on bone.

Both treatments were well tolerated, although OHC appeared to be better tolerated than CC and there was a lower rate of withdrawals due to ADRs in OHC patients. The rates of ADRs observed are similar to those reported in a 4-year follow-up study which evaluated the role of OHC in the prevention of bone loss<sup>24</sup>. The presence of ADRs is important as this can affect treatment adherence, as reported in a study which showed a statistically significant association between the incidence of adverse effects and reduced adherence to calcium and vitamin D supplementation in patients attending centers specializing in osteoporosis<sup>25</sup>.

### Limitations and strengths

Limitations of this study include the fact that treatments were non-randomized. Although randomized controlled trials are considered the gold standard for evaluating the effectiveness of medical interventions, observational studies have strengths as well, particularly when the aim is to investigate efficacy and safety in conditions of real-world practice. The risk of bias in the study was reduced by the fact that there were no significant differences between the two study groups at baseline and treatment compliance between both groups was similar, ensuring comparability. Further strengths of the study included the long-term follow-up and the fact that this is the largest sample to date in which the long-term safety and efficacy of OHC and CC have been compared in a population of perimenopausal women.

A dropout rate of 57.7% could also be considered a limitation of the study, although those levels of dropout are frequently observed in clinical practice<sup>26–28</sup>. The majority of the dropouts were due to loss to follow-up, although adverse effects and concomitant diseases were also reported. Nevertheless, the final sample was sufficiently large to detect statistically significant differences between study groups on the outcomes of interest.

Finally, as the study was intended to assess efficacy and tolerability in real-world clinical practice, the DXA tests were carried out in health centers located in the cities where the patients lived rather than in a sole location. This could have led to slight differences in the coefficient of variation

between centers due to the use of different bone densitometers. Nevertheless, this is likely to have had only a limited influence on the results and any potential bias due to the use of different densitometers across centers can also be assumed to affect both groups equally. It is also relevant to note that the 3.1% reduction in lumbar BMD in the CC group in comparison with the OHC group is likely to be clinically relevant, as it is greater than the 2.6% difference observed in the MORE study between raloxifene and placebo, which was shown to be associated with increased risk of vertebral fracture in the placebo group<sup>29</sup>.

### Conclusions

This study has shown that OHC appears to be significantly more effective than CC at preventing bone loss in the perimenopausal period. Both drugs had a good long-term safety profile although OHC appeared to be better tolerated than CC, especially as regards gastrointestinal events. Given that the calcium dose was approximately 40% higher in the CC group, the superior efficacy of OHC appears to be connected with its ossein constituent. Further research is warranted to confirm the results observed in this study.

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### Ethical statement

All study participants gave informed consent to participate in this research. The study was conducted in accordance with the ethical standards set forth in the Helsinki Declaration (1983). The study was approved by the Spanish Health Authorities.

**Potential conflict of interest** C.C.-B. has disclosed that he has been a recipient of research/grant funding from, has been a consultant/advisor to, and/or has been a lecturer for Gebro, Gedeon Richter, Isdin, Kern, Lacer, Pierre Fabre, Schering Plough, and Shionogi. S.P. has disclosed that he has been a recipient of research/grant funding from, has been a consultant/advisor to, and/or has been a lecturer for Amgen, Bayer-Schering, Exeltis, Gedeon Richter, MSD, Novo Nordisk, Pfizer, Pierre Fabre, Procare Health Serelys, Servier, Shionogi, and Teva. J.M. is a medical advisor with Pierre Fabre Ibérica S.A., a company that commercializes an OHC. The other authors do not declare conflicts of interest.

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